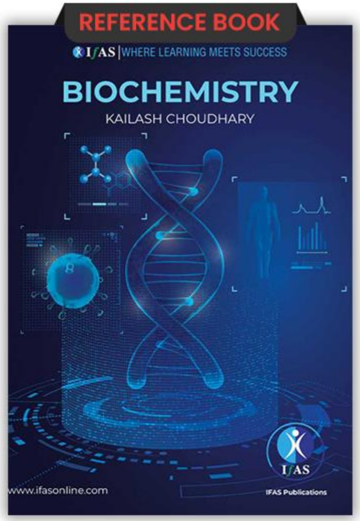
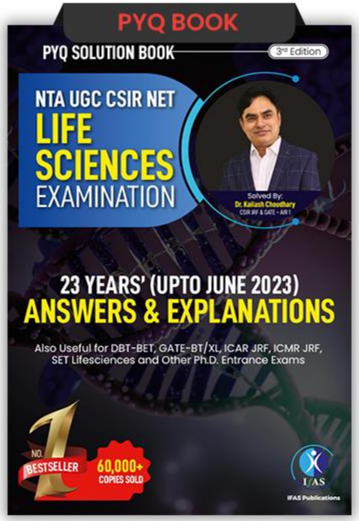
"It doesn't matter what other's are doing, it matters what you are doing"

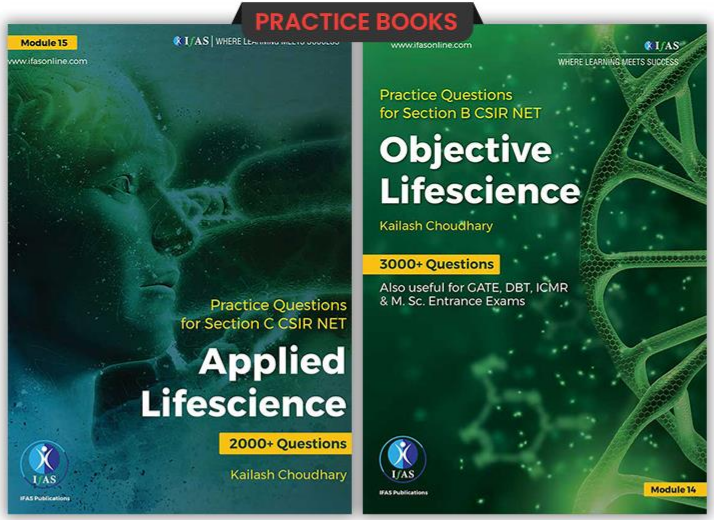
CSIR NET – Life Science

Unit 1: Biochemistry

14 Carbohydrate Metabolism







Points to be covered in this Lecture

- Pasteur Effect
- Warburg Effect
- Linkage Step
- TCA Cycle
- Gluconeogenesis
- Pentose Phosphate Pathway
- Glycogen Metabolism

Pasteur Effect:

- Presence of oxygen decreases the rate of glycolysis. (fermentation)
- More ATP in presence of oxygen inhibits glycolysis

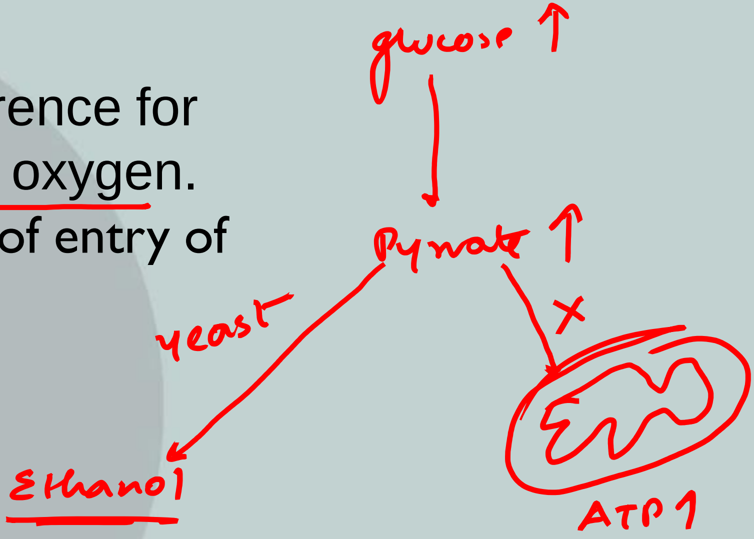
mitochondria

↑ ATP ⊣ PFK-1

↑ ATP ⊣ Pyruvate kinase

Crabtree Effect:

- High glucose concentrations lead to a preference for glycolysis even in the presence of adequate oxygen.
- More ethanol is produced from glucose instead of entry of pyruvate into mitochondria
- Observed in yeast under high external glucose concentration



Warburg effect in cancerous cells:

- The enhanced conversion of glucose to lactate observed in tumor cells,
- Even in the presence of normal levels of oxygen

HIF 1 α

Glycolysis enzyme gene over expression

more enzyme

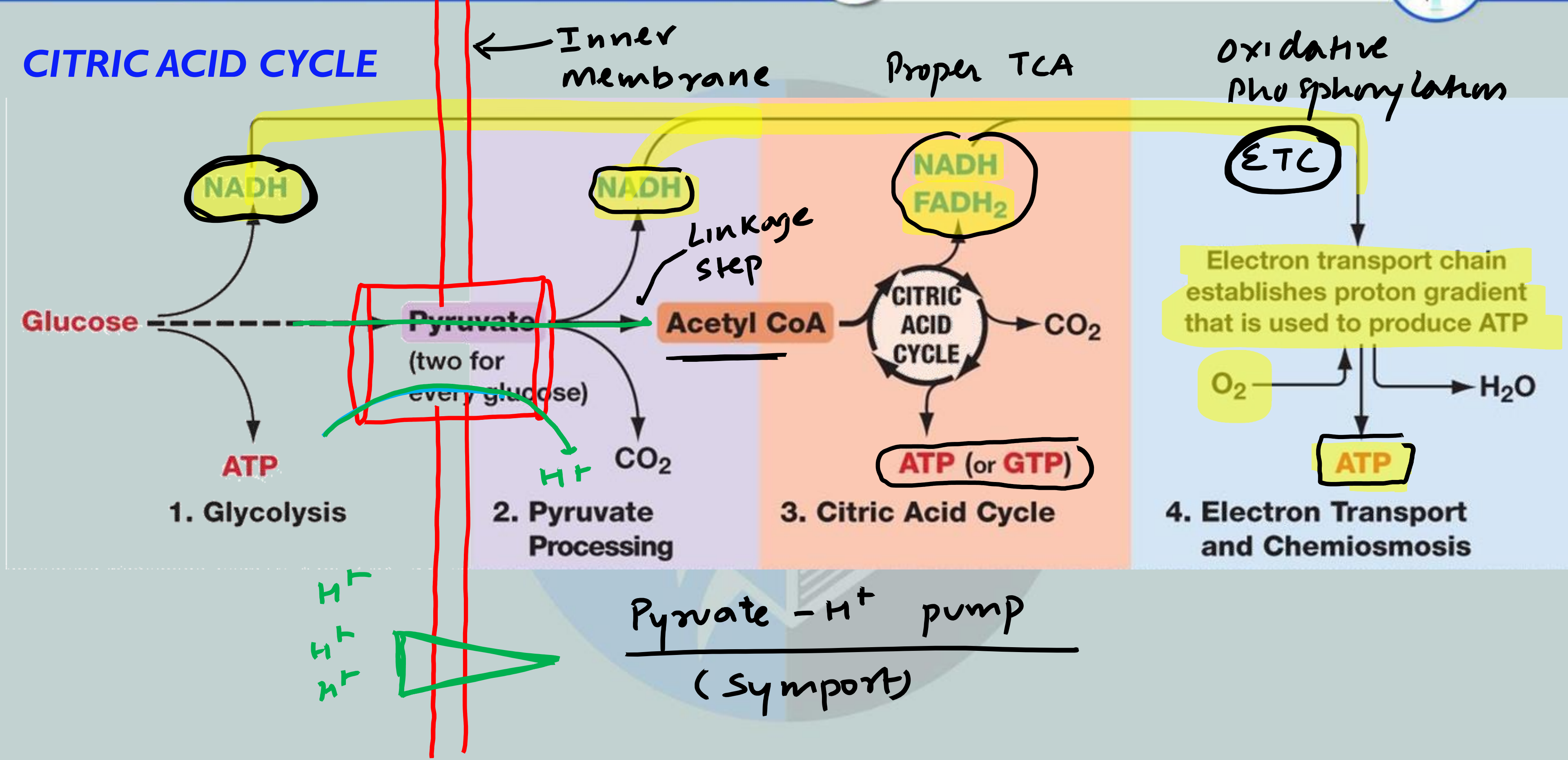
Vmax ↑

Rapid Glycolysis

Pyruvate ↑

Lactate

CITRIC ACID CYCLE



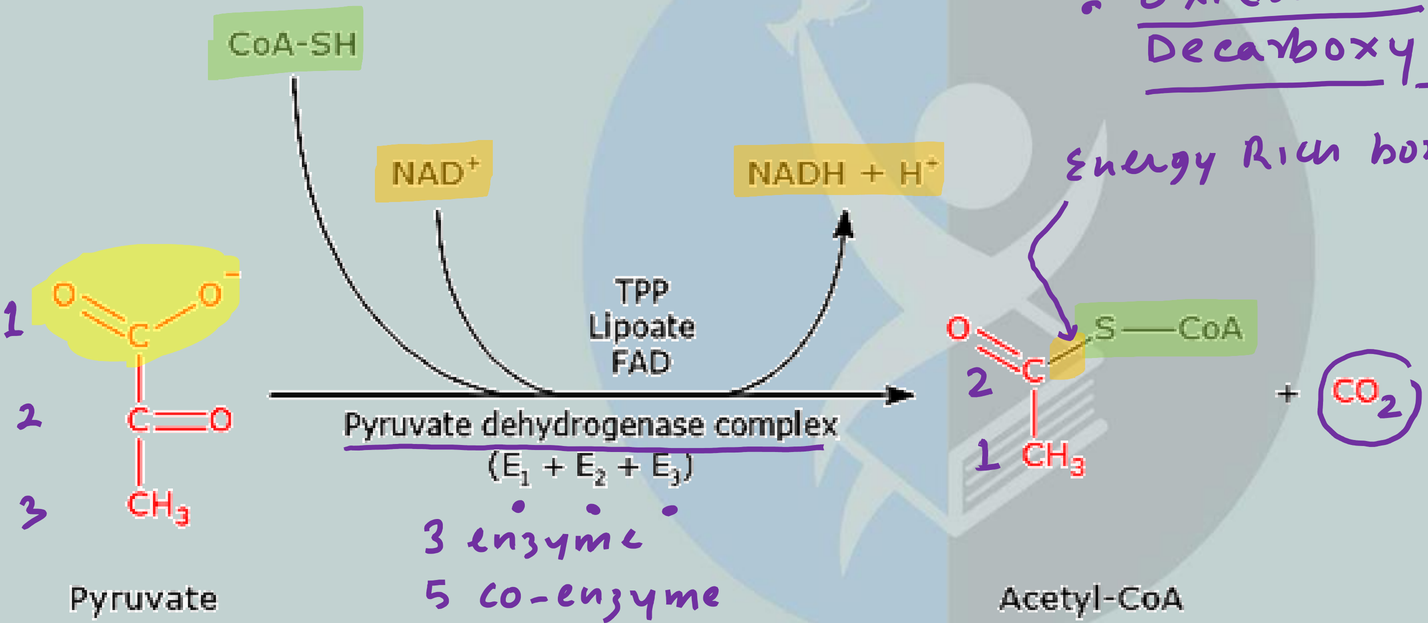
Linkage Step

Conversion of pyruvate into acetyl CoA (Energy Rich molecule)

3 c 2 c

• Oxidative Decarboxylation

Energy Rich bond (Thioester bond)



The pyruvate dehydrogenase multienzyme complex (PDC) consists of 3 enzymes:

1. **Pyruvate dehydrogenase** (E_1) — TPP
2. **Dihydrolipoyl transacetylase** (E_2) — Lipoamide, co-enz A
3. **Dihydrolipoyl dehydrogenase** (E_3) — FAD, NAD$^+$

The five coenzyme required by this complex are

E_1: TPP
E_2: lipoamide and coenzyme A
E_3: FAD and NAD

⊖

Arsenic compounds sequester lipoamide

Regulation of PDH complex

1. Product inhibition by NADH and acetyl-CoA

$$\text{Pyruvate} + NAD^+ \xrightarrow{PDH} \text{Acetyl-CoA} + NADH + CO_2$$

⊖ ⊖

Acetyl CoA ↑

Sensory Kinase (active)

2. Covalent modification of the pyruvate dehydrogenase (E_1) subunit

- Phosphorylated form: **Inactive** ← 
- Dephosphorylated form: **Active**

CITRIC ACID CYCLE

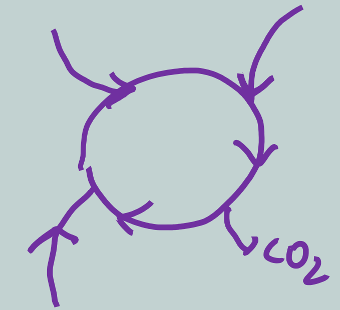
Krebs cycle or tricarboxylic acid (TCA)

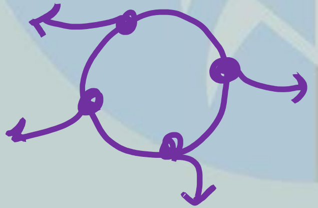
Location: mitochondrial matrix in eukaryotes, cytosol of prokaryotes

Amphibolic in nature

ATP = ↓ NADH = ↓ : Catabolic cycle

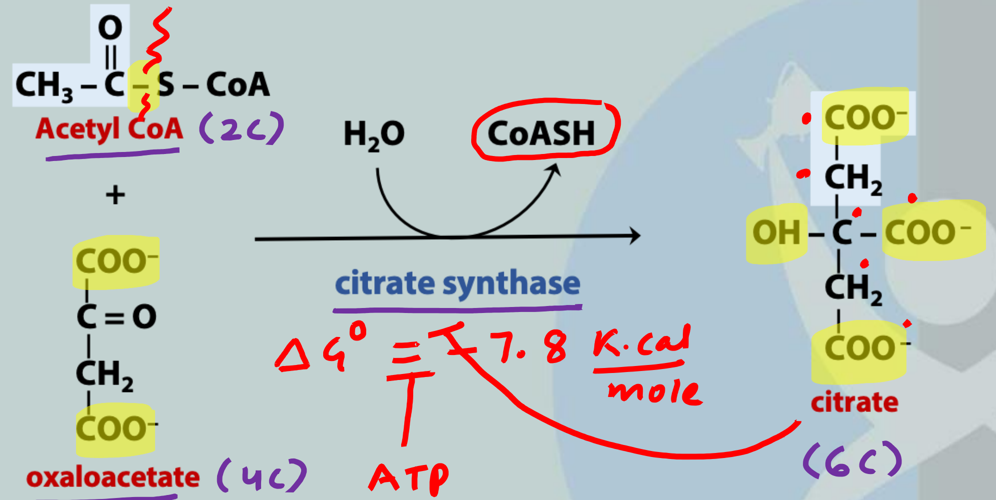
ATP = ↑ NADH = ↑ : Anabolic cycle





Step 1: Formation of citrate (Tricarboxylic acid)

$Asp \xrightarrow[O_2]{NH_2} OAA$



$\Delta G^0 = -7.8 \frac{K.cal}{mole}$

ATP

cytosol

citrate

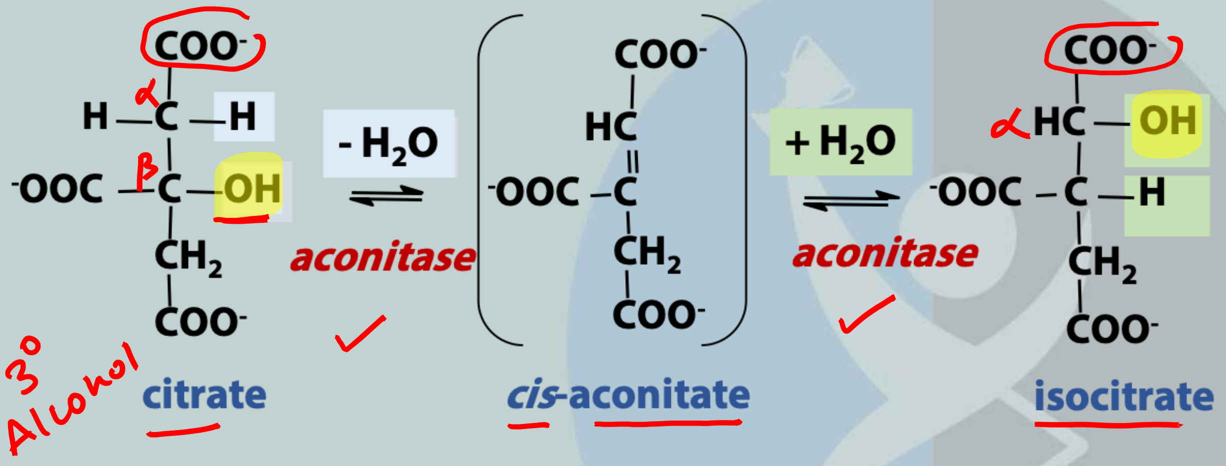
PFK-1

Citrate inhibits phosphofructokinase I (glycolysis) and activates acetyl CoA carboxylase (fatty acid synthesis).

Inhibitor: citrate, ATP (the K_m for acetyl CoA is raised as the level of ATP rises).

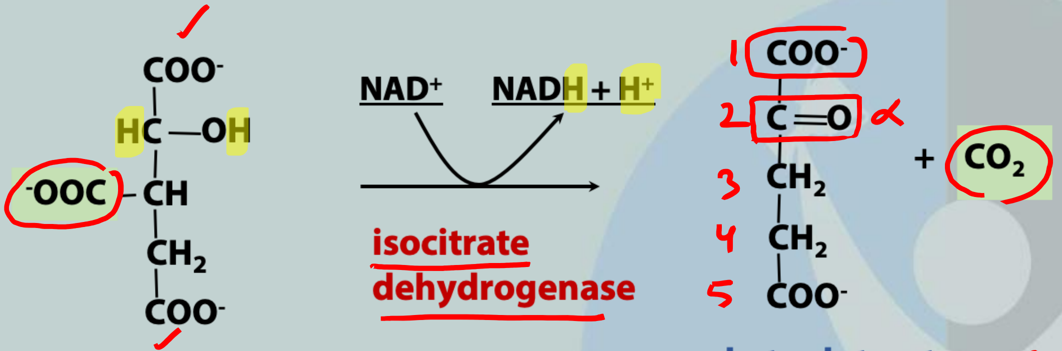
Step 2: Isomerization of citrate to iso-citrate

C—OH



2° Alcohol

Step 3: Formation of α-ketoglutarate by Isocitrate dehydrogenase (ICD)



isocitrate
6 C

α-ketoglutarate , 2-oxo-glutarate
5C

Oxidative Decarboxylation

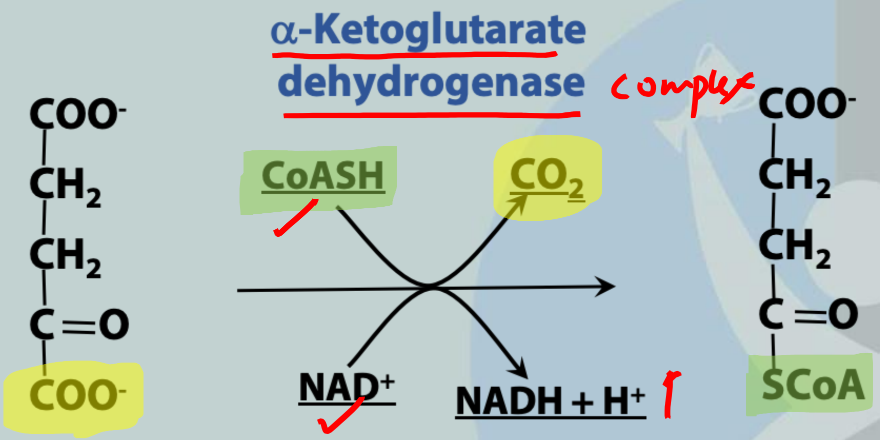
$$\text{Glutamate} \underset{NH_2}{\overset{O_2}{\rightleftharpoons}} \alpha\text{-Keto Glutarate}$$

- Irreversible step

Regulatory step

Inhibitor: NADH, ATP
Activator: ADP.

Step 4: Conversion of α-ketoglutarate to succinyl CoA by α-KGDH



α-Ketoglutarate

TPP, FAD, lipoate

↑succinyl CoA (4C)

- Oxidative Decarboxylation
- Irreversible

E_1 : TPP

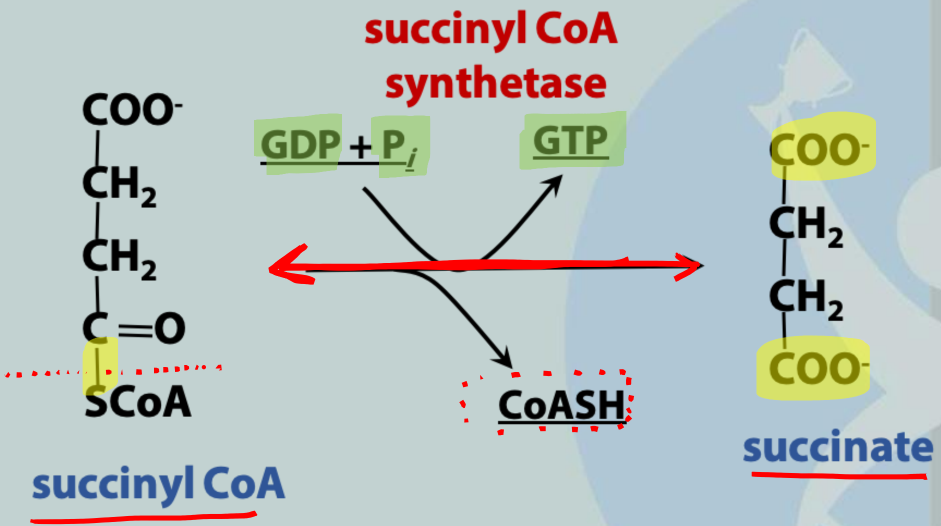
E_2 : Lipoamide, Co-enz A

E_3 : FAD, NAD^+

- 3 enzymes (E_1, E_2, E_3)
- 5 co-enzymes
- Energy Rich molecule

Inhibitor: NADH and succinyl CoA.

Step 5: Formation of succinate by succinyl-CoA synthetase



Substrate Level Phosphorylation

GDP ⟶ GTP (Animals)

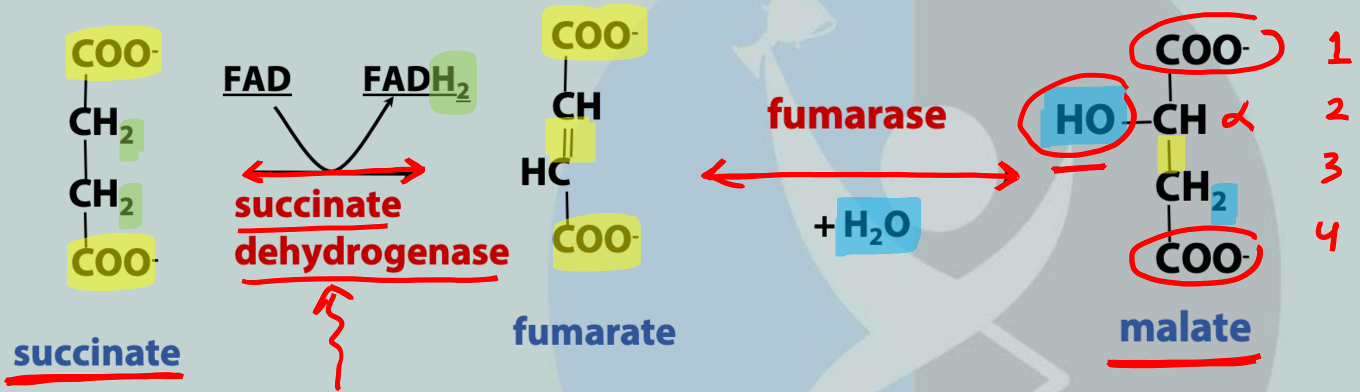
ADP ⟶ ATP (Plant, bacteria)

Mammals: GTP

plant and bacteria: ATP

Step 6: Conversion of succinate to fumarate by SDH : oxidation

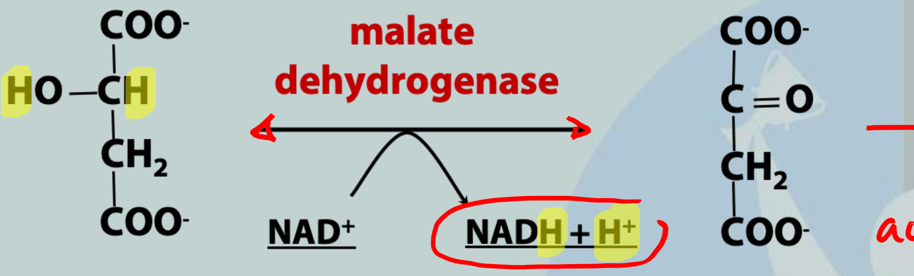
Step 7: Formation of malate by fumarase : Hydration



- Inner membrane of mitochondria
- FAD ⟶ $FADH_2$
- Inhibitor : Malonate

Step 8: Conversion of malate to oxaloacetate by MDH

• oxidation step



malate $\Delta G^\circ = +7.1$ K Cal

oxaloacetate $\Delta G^\circ = -7.8 \frac{\text{K.cal}}{\text{mol}}$

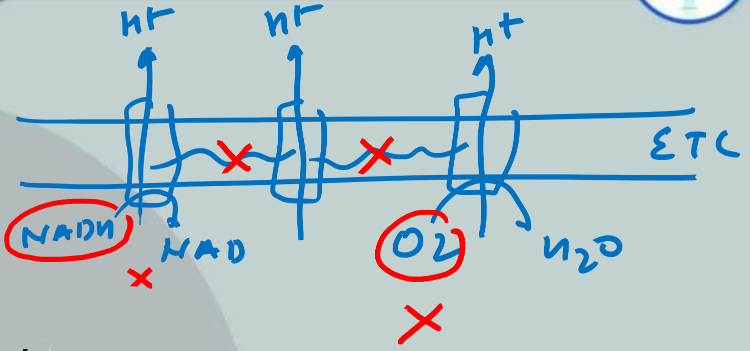
citrate synthase

acetyl coA → citrate

co-enz A

$$\Delta G^\circ_{overall} = \Delta G^\circ_1 + \Delta G^\circ_2$$
$$= (+7.1) + (-7.8)$$
$$= 7.1 - 7.8$$
$$= -0.7 \text{ K.cal/mole.}$$

Requirement of O_2 by TCA cycle:



Indirect Requirement for Oxygen:

- Without oxygen, the ETC cannot operate
- NAD^+ and FAD regeneration cannot be observed
- TCA cycle would not function

O_2 absent

$NADH = \uparrow \xrightarrow{\times} NAD^+ \downarrow$

$FADH_2 = \uparrow \xrightarrow{\times} FAD \downarrow$

Summary of TCA cycle:

1 Pyruvate = 12.5 ATP

The events of Krebs cycle may be summarized as

(2C) 1 1 1 1

$$\text{Acetyl CoA} + 3\ NAD^+ + FAD + GDP + Pi + 2H_2O \rightarrow$$

1 1

$$2CO_2 + 3NADH + 3H^+ + FADH_2 + GTP + CoA$$

1 Acetyl CoA ⟹ 10 ATP equivalent energy

Energetics of TCA cycle:

3 NADH × 2.5 ATP = 7.5 ATP

1 $FADH_2$ × 1.5 ATP = 1.5 ATP

1 GTP × 1 = 1 ATP

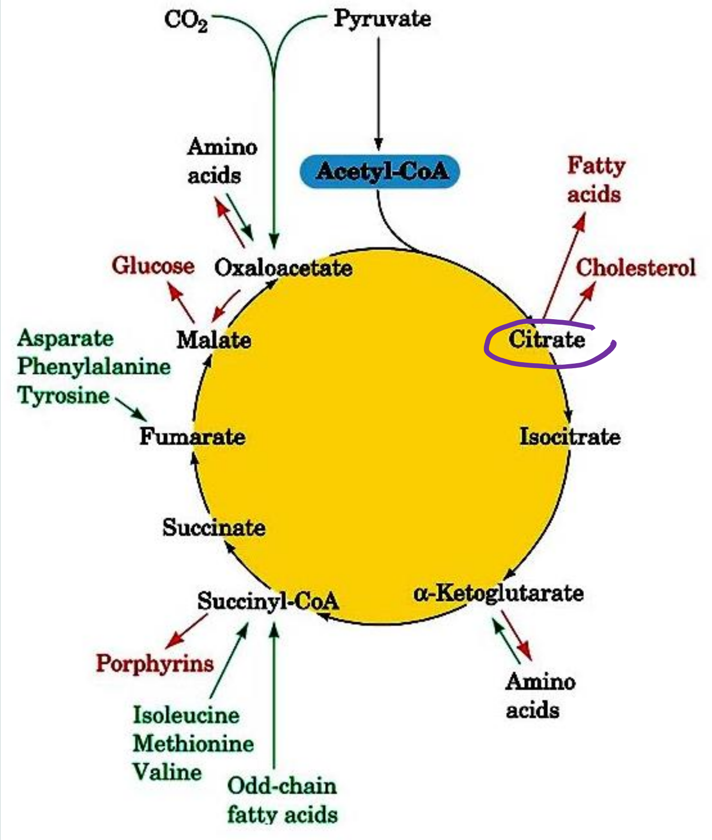
$\boxed{10\ ATP}$

1 Pyr ⟶ 1 Acetyl CoA

1 NADH

Amphibolic nature of the citric acid cycle

Cataplerotic: out
Anaplerotic: in



- Anaplerotic Rx^n
  Synthesis of TCA cycle intermediate
  ATP = ↓, NADH = ↓
- Cataplerotic Rx^n
  - Decrease of TCA cycle intermediate
  - ATP = ↑, NADH = ↑

Gluconeogenesis

Animals cannot convert acetyl CoA into glucose.

Purpose: Synthesis of glucose from non-carbohydrate precursors.

Precursor: Lactate, Pyruvate, Amino acids, Glycerol, Pyrimidine, Propionyl coA

Pathway: The reversal of glycolysis bypassing irreversible steps.

Glucose ⇅ Pyruvate

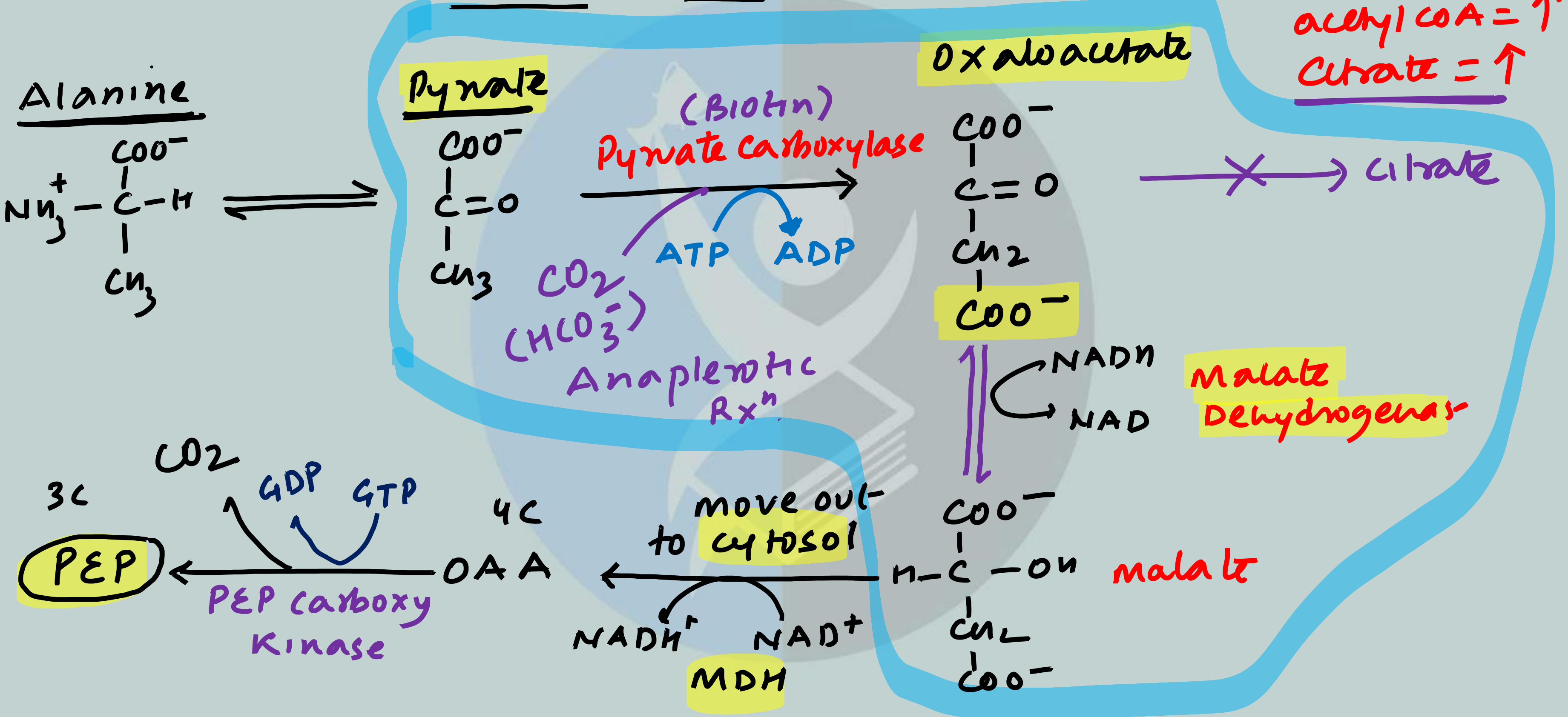
Site: The liver and kidney (mitochondria, Cytosol and ER), intestinal cells

Condition: Blood glucose level low, Glucagon

Regulation: Glycolysis and gluconeogenesis are reciprocally regulated

Cellular condition: ATP = ↑ Acetyl CoA = ↑
NADH = ↑ Citrate = ↑

Stage I: Conversion of Pyruvate to PEP



Reversible

Stage 2: Conversion of PEP to F16BP

Stage 3: Conversion of F16BP to G6P

Fructose 16 Bis phosphate

F16 Bis Phosphatase — P
(active)

IP

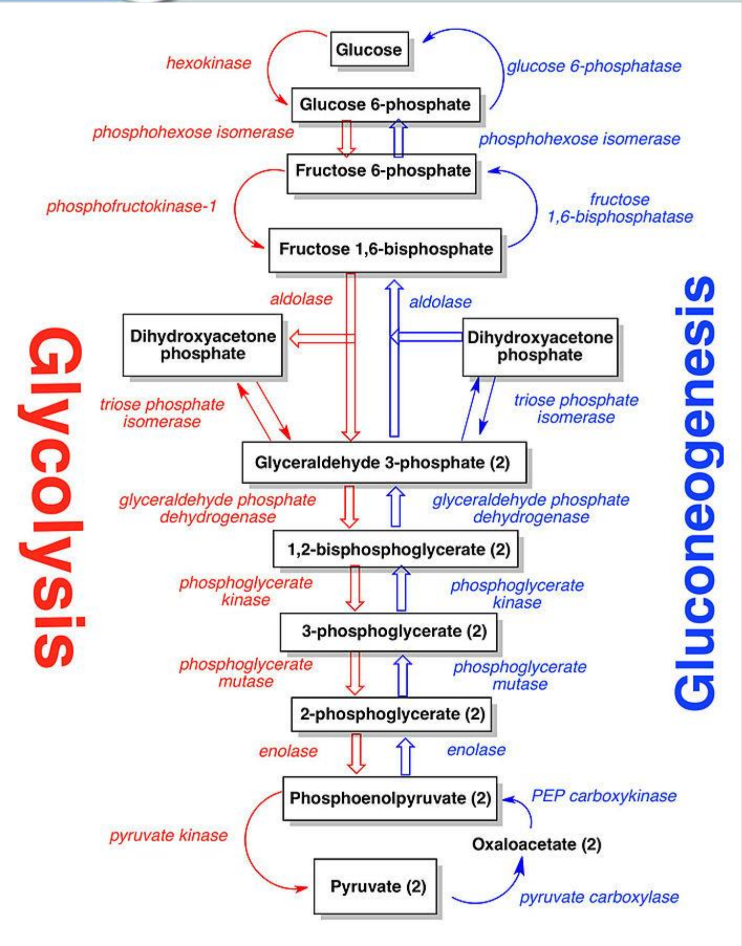
Fructose-6-P

Isomerase

Glucose-6-P

×

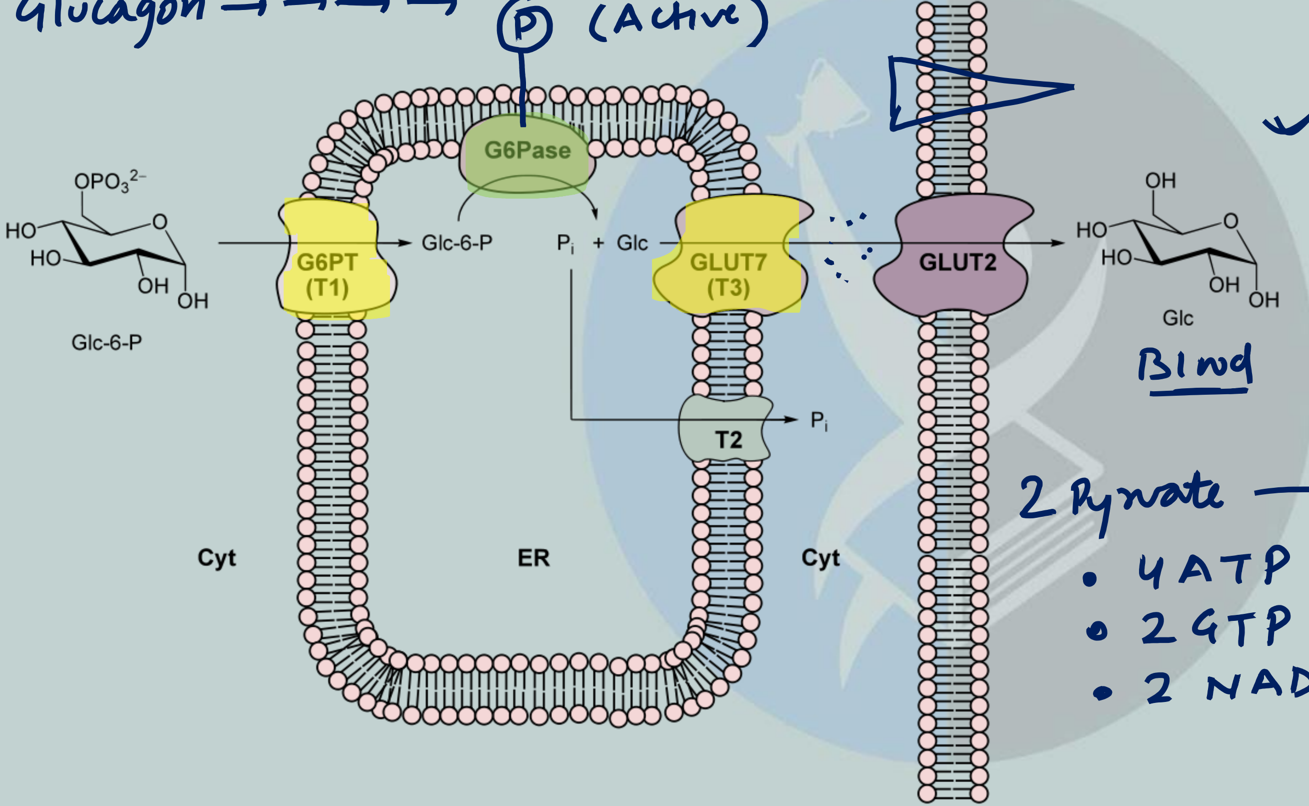
Glucose



Stage 4: Conversion of G6P to Glucose

: Glucose-6-Phosphatase
→ SER of liver & Kidney.

Glucagon → → → → P (Active)



Blood

✓ GLUT-2 : Liver
GLUT 4 : Muscles

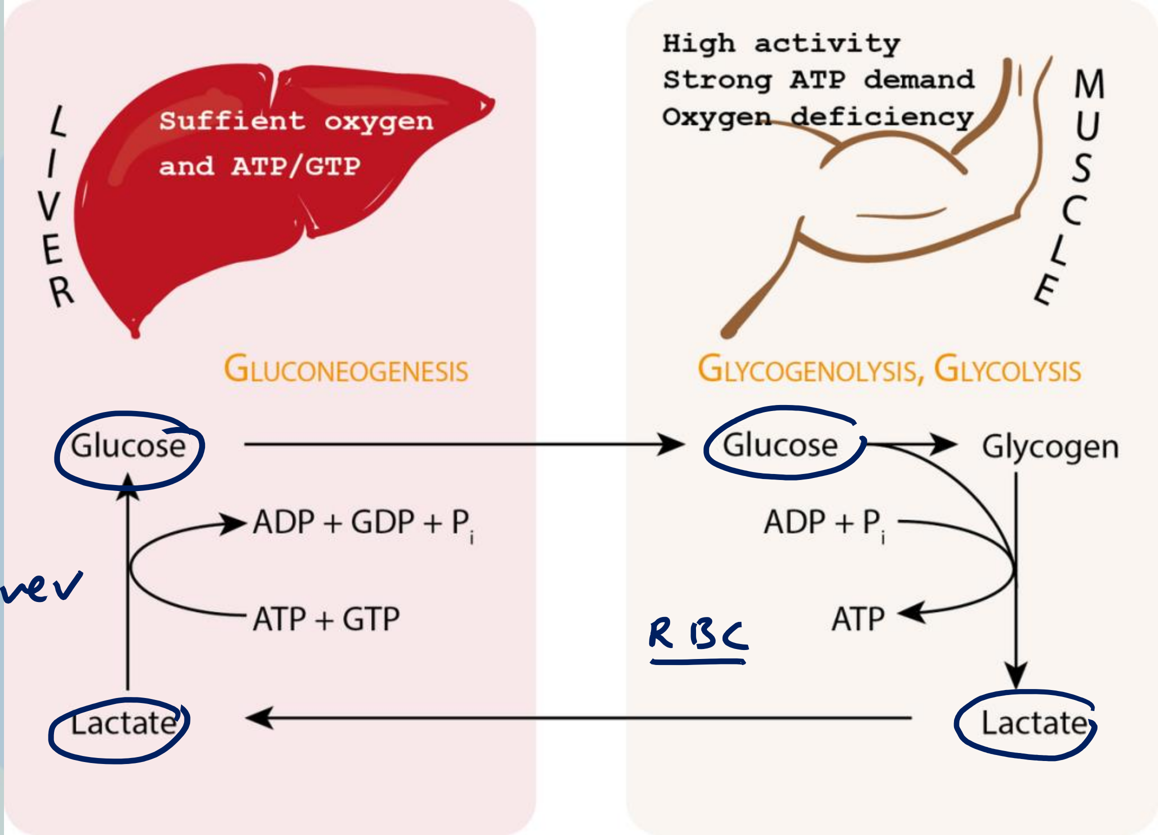
2 Pyruvate → 1 Glucose
- 4 ATP
- 2 GTP
- 2 NADH

} Investment

Cori-Cycle:

Lactate produced from glucose under anaerobic conditions in muscles and RBC is transported to liver converted into **pyruvate** then into glucose

Liver



RBC

PENTOSE PHOSPHATE PATHWAY or HEXOSE MONOPHOSPHATE SHUNT

Alternative pathway to glycolysis for the oxidation of glucose.

Location: Cytosol

Provides: NADPH and Ribose-5-phosphate

Purpose of Pentose Phosphate Pathway

→ Also provide pentose phosphate sugar → Nucleotide biosynthesis

NADPH : Anti-oxidant machinery of RBC

$O_2 \rightarrow H_2O_2 \rightarrow 2H_2O$, O_2

Glutathione Peroxidase

Glutathione (Reduced)

Glutathione (oxidized)

Glutathione Reductase

NADP

NADPH

HMP

H_2O_2 → oxidize

- membrane lipids of RBC
- Hemolytic anemia

- Biosynthesis of aa, fatty acid, cholesterol, nucleotides
- Detoxification rxn by cyt P 450 (SER of liver)
- Phagocytotic cells → oxygen dependent killing

1 2 3

Consists of three stages – **Oxidation, Isomerization and Regeneration** - in which NADPH is produced, pentose undergo isomerization, and glycolytic intermediates are recovered.

$NADP \rightarrow NADPH$

various pentose phosphate sugar

Stage I: Oxidative phase:

Step I: Glucose 6 Phosphate dehydrogenase ⊣ ⊖ NADPH

$$\text{Glucose-6-P} \xrightarrow{NADP^+ \rightarrow NADPH} \text{6-Phospho-}\delta\text{-Gluconolactone}$$

$$\xrightarrow{H_2O} \text{6 Phospho-Gluconate}$$

$$\xrightarrow{NADP \rightarrow NADPH,\ CO_2} \text{Ribulose-5-P}$$

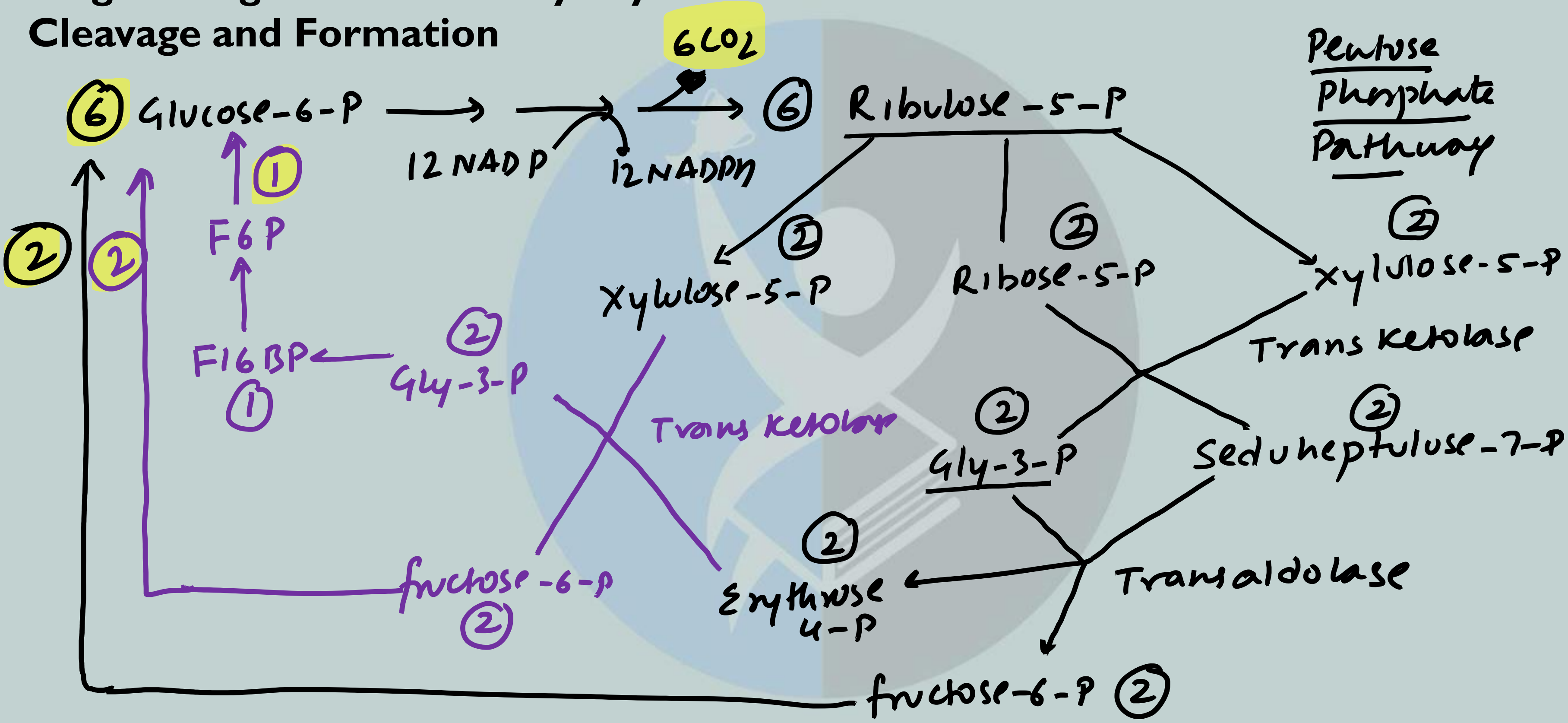
Step 2 & 3: 6-Phosphogluconolactonase and 6-Phosphogluconate dehydrogenase

$$\underset{(6C)}{1\ \text{Glucose}} \xrightarrow[CO_2]{2\,NADP \rightarrow 2\,NADPH} \underset{(5C)}{1\ \text{Ribulose-5-P}}$$

Stage 2: Isomerization and Epimerization of Ribulose-5-Phosphate

$$\text{Xylulose 5 P} \xrightleftharpoons{\text{Epimerase}} \text{Ribulose 5 P} \xrightleftharpoons{\text{Isomerase}} \text{Ribose 5 P}$$

Stage 3: Regeneration of Glycolytic intermediates involves Carbon–Carbon Bond Cleavage and Formation



Glucose-6-Phosphate Dehydrogenase Deficiency : X- Linked Recessive disorder

- No NADPH Production
- H_2O_2 = ↑
- Hemolytic anemia

- cannot consume → vicia faba
  favism
- Sensitive to anti malarial drugs.

Glutathione peroxidase, reductase
Favabeans (vicia faba), primaquine

Glycogen Biosynthesis

Location: Liver and Muscles (Cytosol)

Physiological Conditions

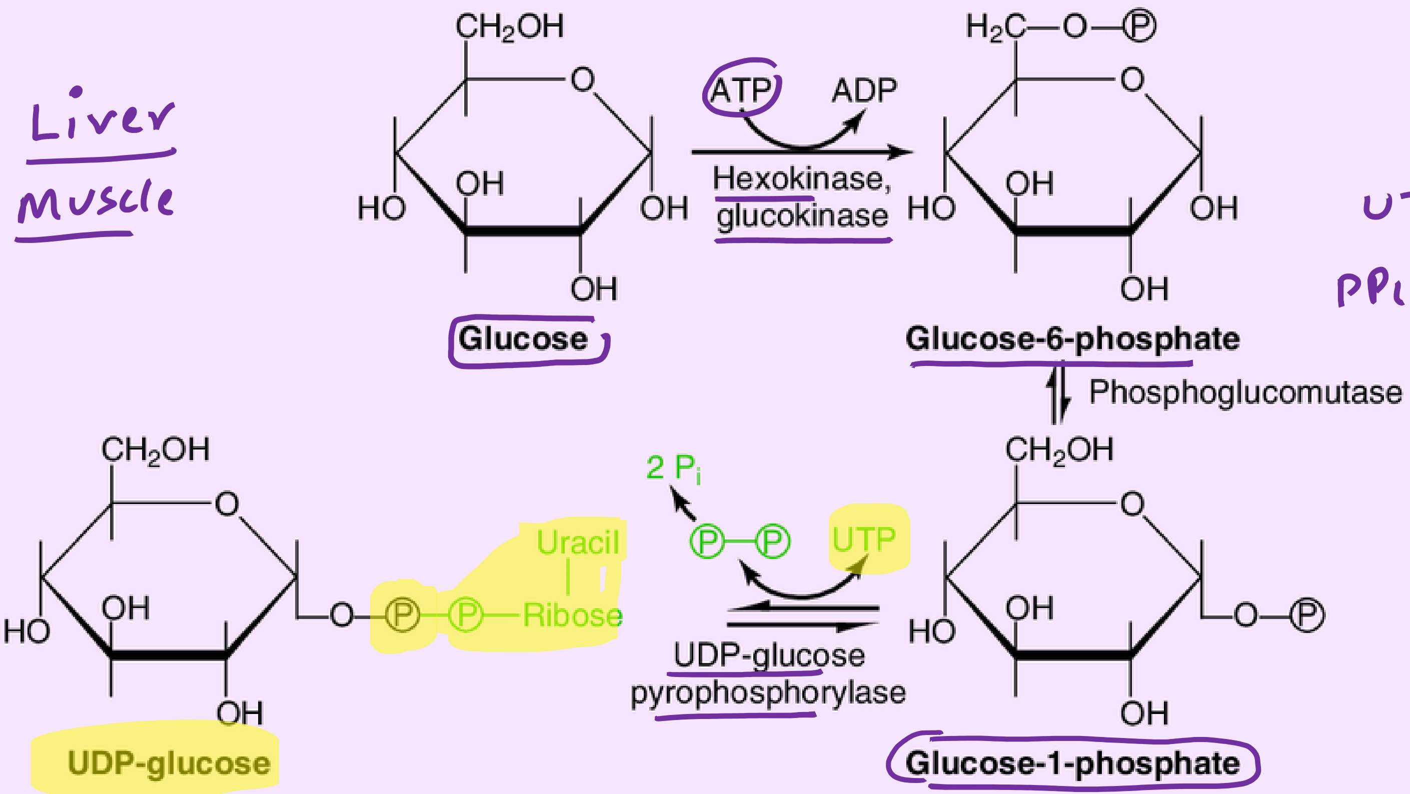
- High Blood Glucose
- Insulin Signaling
- ATP High
- NADH High
- Glucose 6 Phosphate high

Active form: UDP Glucose

1. Synthesis of active glucosyl unit: UDP-Glucose

Liver

Muscle



G6-P

⇅

G1P

UTP

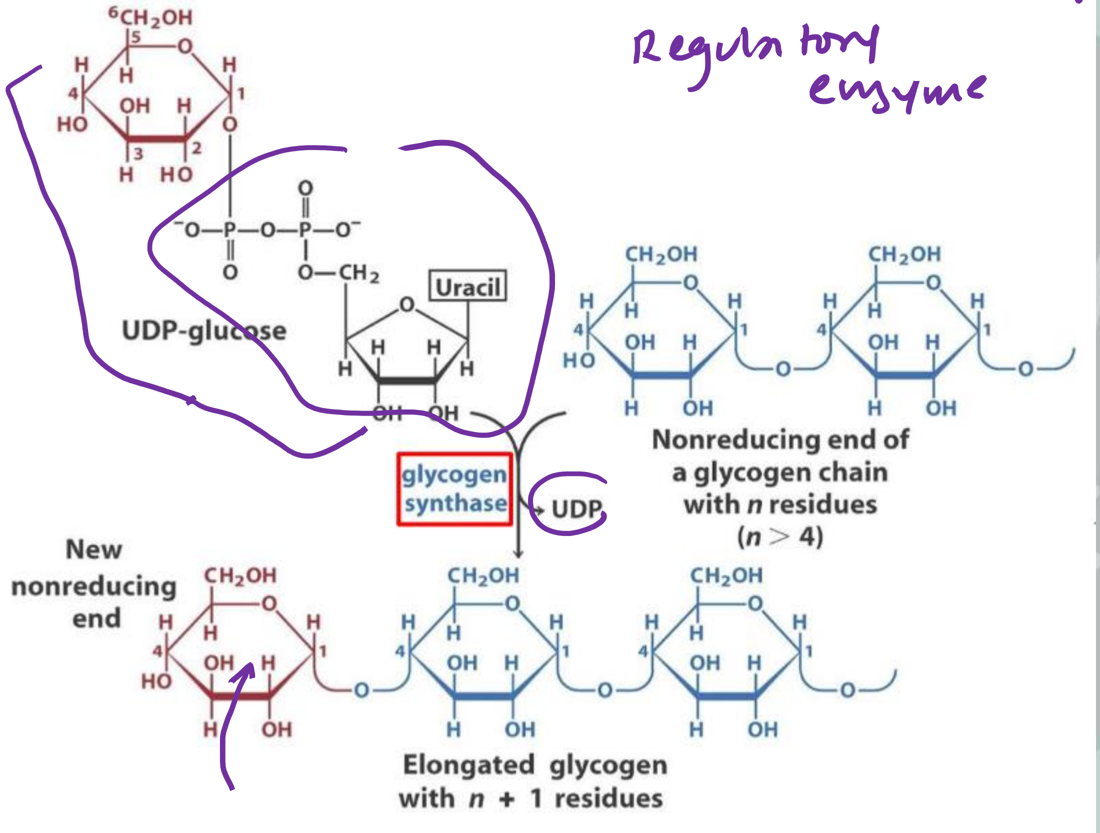
PPi

UDP-Glucose Pyrophosphorylase

UDP-Glucose

2. Glycogen extension by glycogen synthase : form α 1→4 glycosidic bond.

Regulatory enzyme

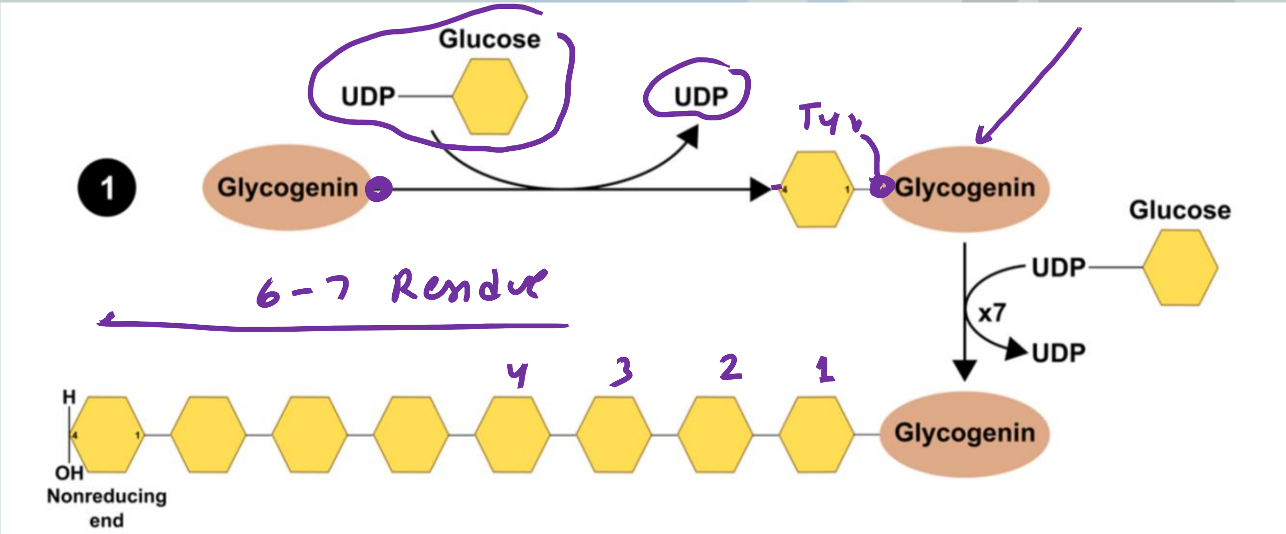


−ve = ADP and Pi, Phosphorylated form (Glucagon/Epinephrine)

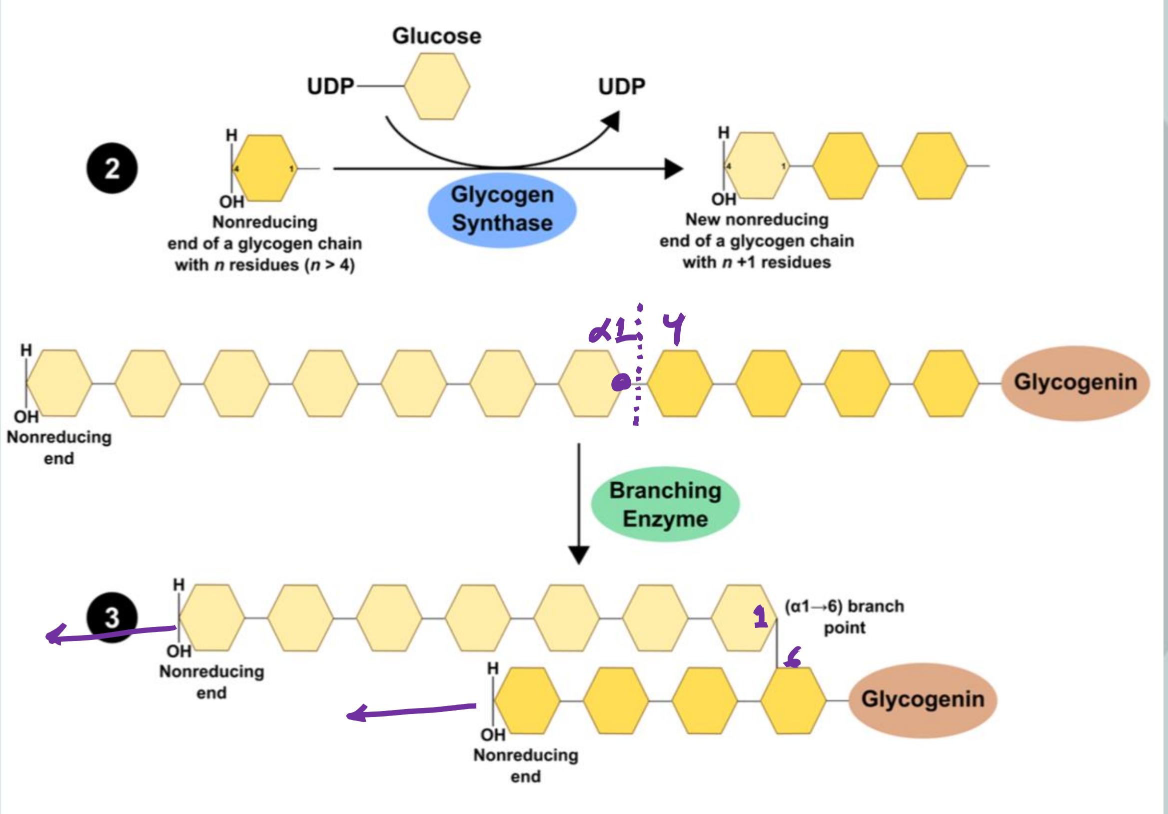
+ = G6P, Dephosphorylated form (Insulin)

3. Glycogenin Primes Glycogen Synthesis

- 349-residue protein
- Acts as a glycosyltransferase
- Attaches a glucose residue donated by UDP-Glucose to the OH group of its Tyr 194
- Extends the glucose chain by up to seven additional UDP Glucose-donated glucose



4. Branching enzyme transfers seven-residue glycogen segments



α 1→4

Branch : α 1→6 bond

Branching enzyme

Break α 1→4 bond & form α 1→6 bond.

The overall reaction of the glycogen synthesis for the addition of each glucose residue is

$$(\text{Glucose})_n + \text{Glucose} + 2\,\text{ATP} \rightarrow (\text{Glucose})_{n+1} + 2\text{ADP} + P_i$$

$$\text{Glucose} \xrightarrow{\text{ATP} \rightarrow \text{ADP}} \text{G6P}$$

$$\text{G6P} \rightleftharpoons \text{G1P}$$

$$\text{G1P} \xrightarrow{\text{UTP}} \text{UDP-Glucose}$$

$$\text{UDP-Glucose} \rightarrow \text{Glycogen } n+1 + \text{UDP}$$

Glycogen Breakdown (Glycogenolysis)

Conversions from glycogen to Glucose-1-P to Glucose-6-P and finally to Glucose.

Physiological Conditions

Liver: Blood glucose = Low
Glucagon signalling

cellular condition = ATP ↑
= NADH ↑

Muscle: contraction
ATP = ↓ , NADH = ↓

• Break α 1 → 4 glycosidic bond

I. Glycogen phosphorylase

$(Glycogen)_n \longrightarrow Glycogen_{n-1} + Glucose\text{-}1\text{-}P$

Pi

⊕ ↑ AMP (muscles)

⊖ ⊥ ATP

P

active

↑ glucagon

↑ Liver

P

$GP_b \longrightarrow GP_a$

Glucagon = active

Insulin = inactive

AMP/P (*Ser 4*): T → R (*active*)

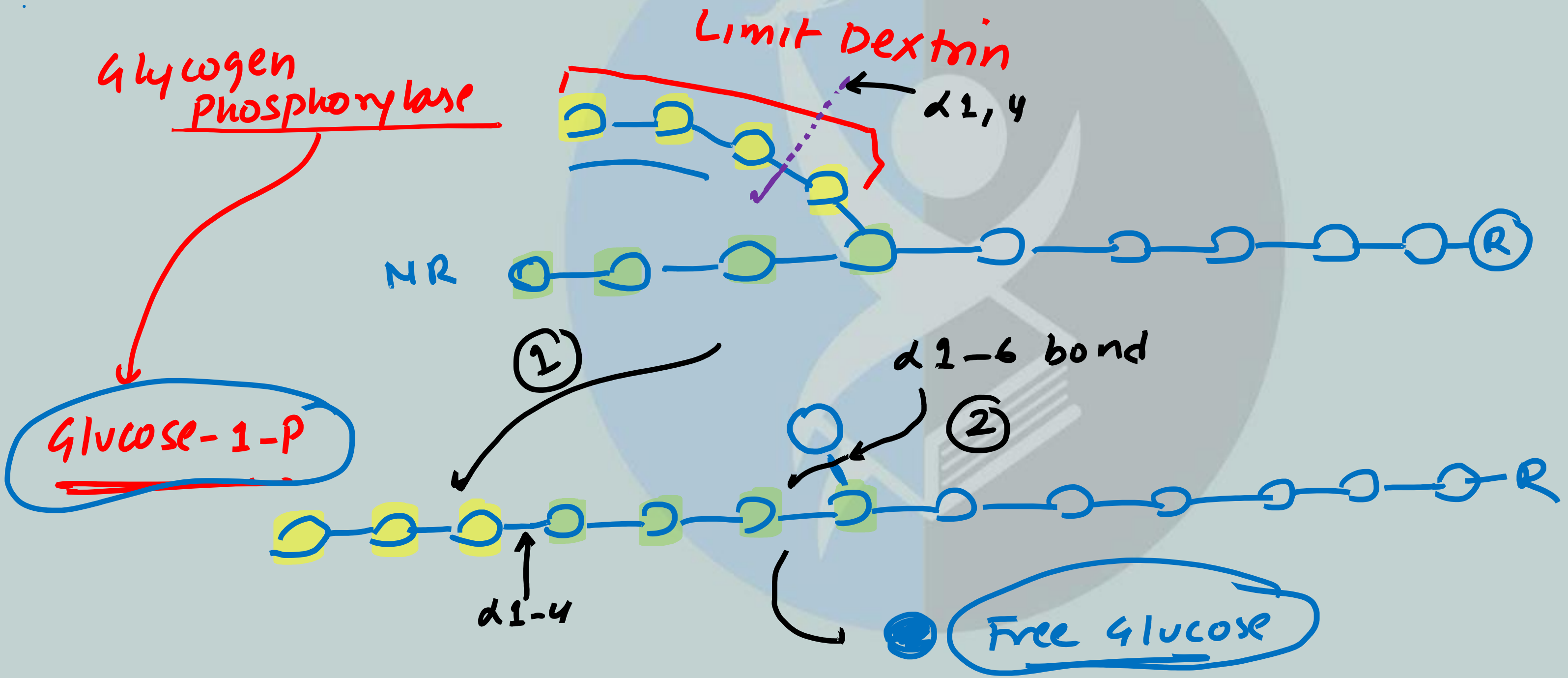
ATP: R → T (*active*)

De-branching Enzyme – Single Bifunctional Enzyme

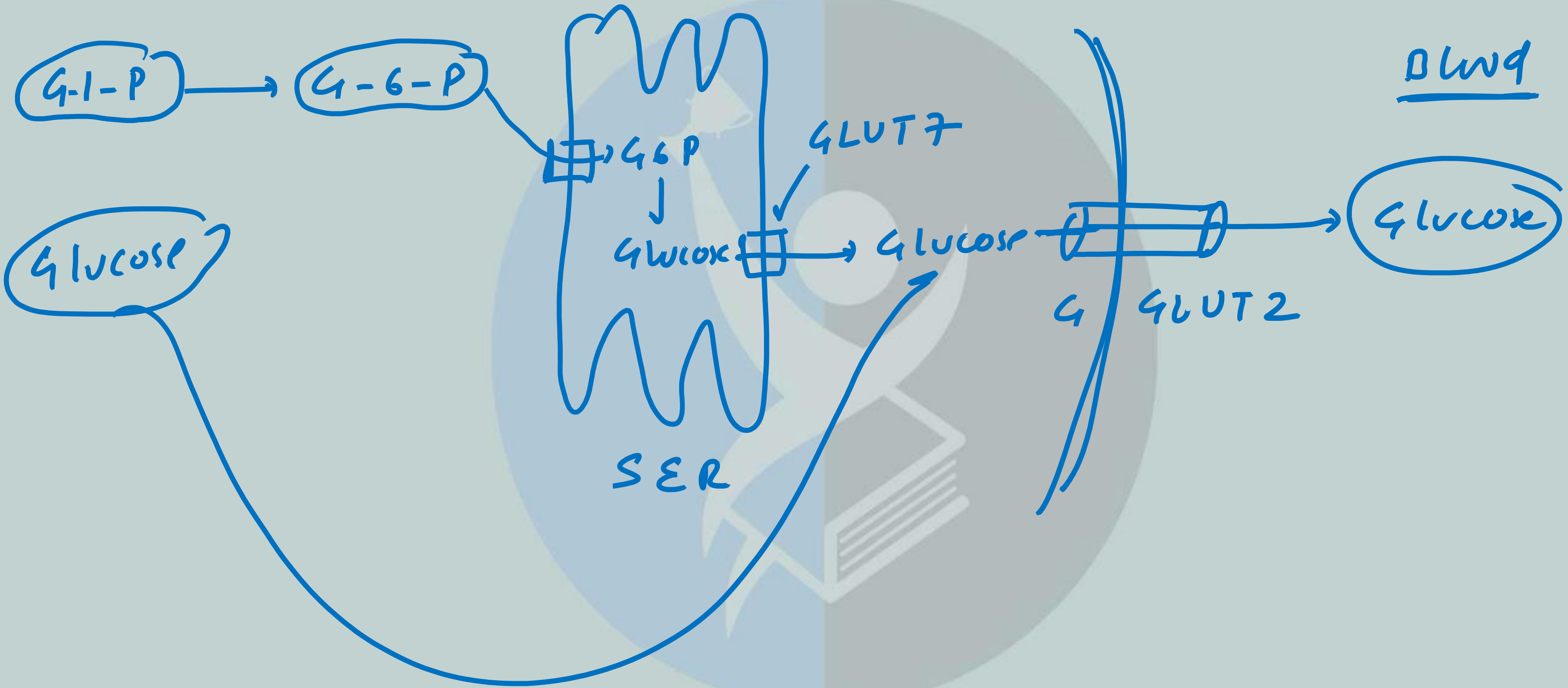
- ($\alpha 1 \rightarrow 4$) Trans-glycosylase (glycosyl-transferase)
- ($\alpha 1 \rightarrow 6$)- *Glucosidase*

9 G-1-P

1 Glucose

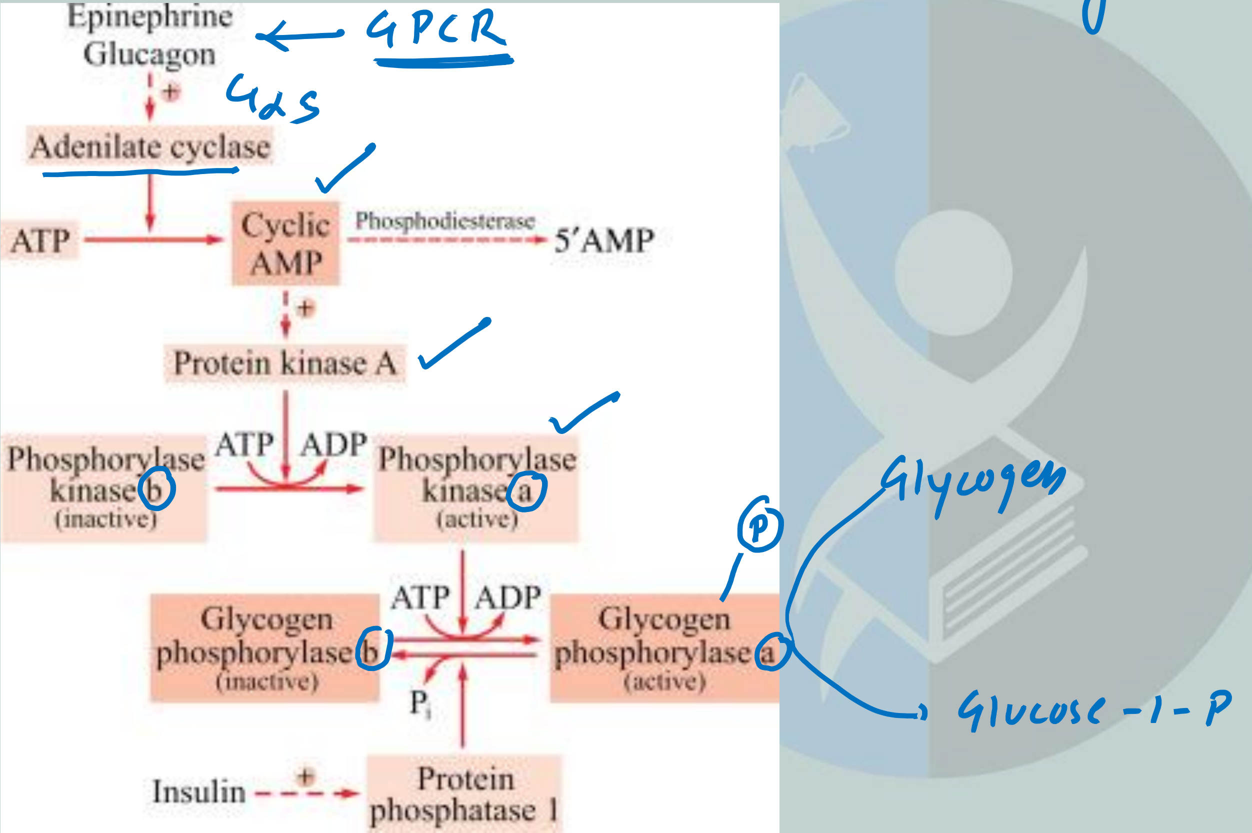


Glucose-6-Phosphatase Generates Glucose in the Liver.



Glucagon/Epinephrine Signaling

← Blood glucose = ↓



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